SIU 7397
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Kathleen C.M. Campbell — Art Unit 1614
Serial No. 10/694,436
Filed October 27, 2003
Confirmation No. 8942
For THERAPEUTIC USE OF METHIONINE TO FOR THE TREATMENT OR PREVENTION OF MUCOSITIS
Examiner Shirley V. Gembeh

**DECLARATION OF PRIOR INVENTION UNDER 37 C.F.R. § 1.131**

I, Kathleen C. M. Campbell declare as follows:

1. I am the inventor of the subject matter claimed in the above-entitled United States patent application.

2. I am submitting this Declaration to establish conception of my invention in the U.S. before March 13, 2003, the filing date of U.S. Provisional Application No. 60/454,886, the priority document for U.S. Patent Application Publication No. 2004/0198841 and thereafter my invention was diligently reduced to practice.

3. I conceived of the invention claimed in this application in the United States before March 13, 2003. To that end, I first had the idea of treating oral mucositis with methionine in subjects exposed to radiation with or without administration of anti-tumor platinum coordination compounds when my stepfather was diagnosed with brain cancer.

4. To aid my development of a protective agent for mucositis, I read the scientific literature to better understand the mechanisms of radiation-induced oral mucositis. However, the tissues of the cochlea and the oral mucosa are quite different. After I read about the mechanisms

of radiation-induced oral mucositis and deliberated on the problem, I concluded that there was a good possibility that methionine would be an efficacious protective agent. Therefore, I contacted two of my oncologist colleagues at Southern Illinois University School of Medicine (SIUSOM) to obtain their opinion and to discuss options for animal models and human clinical trials to test my hypothesis.

5. Dr. James Malone is an otolaryngologist in SIUSOM's Division of Otolaryngology and Department of Surgery, who specializes in Head and Neck Oncology. Dr. Elizabeth Peralta, is a general surgeon in SIUSOM's Department of Surgery with a special interest in cancer care. Dr. Peralta's research concerns cancer prevention through nutrition and weight control. Therefore, I asked these two oncologists to meet with me to discuss my idea.

6. On October 7, 2002, Dr. Malone came to my research laboratory where I provided him with a brief review of the current status of my ongoing research. I told him about my idea to use methionine to protect against radiation-induced oral mucositis and asked him about current palliative therapies and clinical care of patients with radiation-induced oral mucositis. He stated that the radiation-induced oral mucositis and dry mouth accompanying it were the biggest clinical complaints of this patient population and little relief was available for it. He felt that an efficacious protective agent would be of great value to these patients. We also talked about the role of cisplatin which he believed exacerbated radiation-induced oral mucositis. From my previous work with cisplatin, I believed that methionine would possibly also ameliorate this exacerbation of oral mucositis. Dr. Malone and I also discussed possible patient populations and animal models for testing, particularly the hamster cheek pouch model. Although he was very interested and supportive, he stated that his short tenure at SIUSOM had not allowed him to sufficiently establish his clinical practice and he was not yet fully familiar with the oncology research program and procedures. Therefore, I suggested that we meet with Dr. Peralta who had already established an active oncology research program.

7. On October 17, 2002, I met with Dr. Peralta, but Dr. Malone did not attend. Therefore, Dr. Peralta and I discussed the project. Because Dr. Peralta does not treat head and neck cancer patients, we primarily discussed my D-methionine protection (particularly otoprotection, neuroprotection and nephroprotection) from the side effects of cisplatin chemotherapy in women with ovarian cancer. Dr. Peralta asked whether it was possible to use methionine as a protectant for breast cancer patients, but since platinum chemotherapeutic compounds are rarely used to treat breast cancer, I told her that I didn't think that would be a likely target population. We then agreed to schedule a meeting for Dr. Malone, Dr. Peralta and myself because we needed Dr. Malone's expertise in head and neck oncology to advance my research idea.

8. On November 12, 2002, Dr. Peralta, Dr. Malone, and I focused on how we might test methionine to prevent and/or treat radiation-induced oral mucositis and the accompanying dry mouth. I discussed the putative mechanisms of methionine protection of normal cells. Dr. Malone talked about animal models and particularly the hamster cheek pouch model. We asked for Dr. Peralta's input regarding therapeutic radiation facilities for animal research. I talked about the difficulty I had in obtaining access to therapeutic radiation facilities for my previous research in radiation-induced hearing loss and stated that I was uncertain that I could conduct the animal experiments at SIUSOM because I believed there were no therapeutic research facilities for animals. Dr. Peralta stated that although she did animal oncology research, she had not been working with radiation and didn't know whether it was possible to conduct such experiments at SIUSOM. We also discussed possible tumor models to test if methionine's protectant efficacy was selective for healthy tissue or if it also protected tumor cells. Dr. Peralta stated that she had never worked with head and neck cancer cell lines or tumor models. Dr. Malone stated that he would be willing to help set that up but he did not have much time to do so. They encouraged me to test methionine as a protectant against radiation-induced oral mucositis. I told them that I

would discuss the idea with scientists from Molecular Therapeutics when I met with them later that week, but before doing so, I wanted to investigate the idea's promise with oncologists. I also stated that I thought that Molecular Therapeutics would have the appropriate facilities and personnel to test my hypothesis and provide the necessary data.

9. On November 14, 2002, I went to Detroit, Michigan. During my visit, there was a meeting wherein Dr. Prasad Sunkara, Dr. Alnawaz Rehemtulla, Dr. Brian Ross, and myself were in attendance at the offices of Molecular Therapeutics. During the meeting, I discussed my data for methionine protection from aminoglycoside ototoxicity and nephrotoxicity, cisplatin-induced hearing loss, neurotoxicity, nephrotoxicity, weight loss and alopecia, and noise-induced hearing loss. I had previously sent them articles to review and they had questions about the data and the literature in the area. I told them that I was very interested in testing whether methionine could protect against radiation-induced oral mucositis, but I could not perform the necessary experiments at SIUSOM. I asked them if they could and would be willing to conduct the experiments at Molecular Therapeutics. They were receptive to performing the experiments and asked about dosing protocols. I told them that I thought a good starting point would be a 300 mg/kg methionine dose. This was the dose that I had found effective for cisplatin otoprotection. That is the dose that they initially used for these experiments at Molecular Therapeutics.

10. Facts in support of this Declaration are attached hereto. Simultaneously submitted herewith are declarations from Dr. James P. Malone and Dr. Elizabeth Peralta describing our meetings wherein we discussed my invention. Also attached are true and correct copies of Dr. Malone's, Dr. Peralta's, and my schedule showing the research meetings where we discussed my invention. As such, these documents evidence my conception of the invention claimed in the application prior to March 13, 2003.

11. My invention was reduced to practice by employees of Molecular Therapeutics as evidenced by the simultaneously submitted declaration of Dr. Alnawaz Rehemtulla.

12. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Kathleen C. M. Campbell

Kathleen C. M. Campbell

3-17-2008

Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Kathleen C.M. Campbell Art Unit 1614
Serial No. 10/694,436
Filed October 27, 2003
Confirmation No. 8942
For THERAPEUTIC USE OF METHIONINE TO FOR THE TREATMENT OR PREVENTION OF MUCOSITIS
Examiner Shirley V. Gembeh

**DECLARATION UNDER 37 C.F.R. § 1.131**

I, James P. Malone declare as follows:

1. I am an assistant professor in the Division of Otolaryngolgy at Southern Illinois University School of Medicine. I am board certified in Otolaryngology and my subspecialty training and expertise are in Head and Neck Surgery and reconstructive surgery of the head and neck. I received his medical degree from The University of Pittsburgh School of Medicine in Pittsburgh, Pennsylvania. I completed my residency in otolaryngology at The Pennsylvania State University in Hershey, Pennsylvania and a fellowship in head and neck surgical oncology and microvascular surgery at The Ohio State University in Columbus, Ohio.

2. On October 7, 2002, I went to Dr. Kathleen Campbell's research laboratory where she gave me a brief review of the current status of her ongoing research. She told me about her idea to use methionine to protect against radiation-induced oral mucositis and asked me about current palliative therapies and clinical care of patients with radiation-induced oral mucositis. I stated that the radiation-induced oral mucositis and dry mouth accompanying it were the biggest clinical complaints of this patient population and little relief was available for it. I told her I believed that an efficacious protective agent would be of great value to these patients. We also talked about the role of cisplatin which I believe exacerbates radiation-induced oral mucositis. Dr. Campbell and I also discussed possible patient populations and animal models for testing,

particularly the hamster cheek pouch model. I was very interested in and supportive of Dr. Campbell's research, but my short tenure at SIUSOM had not allowed me to sufficiently establish my clinical practice and I was not yet fully familiar with the oncology research program and procedures. Therefore, Dr. Campbell suggested that we meet with Dr. Peralta who had already established an active oncology research program.

3. On November 12, 2002, Dr. Peralta, Dr. Campbell, and I focused on how we might test methionine to prevent and/or treat radiation-induced oral mucositis and the accompanying dry mouth. Dr. Campbell discussed the putative mechanisms of methionine protection of normal cells. I talked about animal models and particularly the hamster cheek pouch model. We asked for Dr. Peralta's input regarding therapeutic radiation facilities for animal research. Dr. Campbell discussed her difficulty in obtaining access to therapeutic radiation facilities for her previous research in radiation-induced hearing loss and stated that she was uncertain that she could conduct the animal experiments at SIUSOM because she believed there were no therapeutic radiation research facilities for animals. Dr. Peralta stated that although she did animal oncology research, she had not been working with radiation and didn't know whether it was possible to conduct such experiments at SIUSOM. We also discussed possible tumor models to test if methionine's protectant efficacy was selective for healthy tissue or if it also protected tumor cells. Dr. Peralta stated that she had never worked with head and neck cancer cell lines or tumor models. I stated that I would be willing to help set that up but I did not have much time available. Dr. Peralta and I encouraged Dr. Campbell to test methionine as a protectant against radiation-induced oral mucositis. Dr. Campell told us that she would discuss the idea with scientists from Molecular Therapeutics when she met with them later that week, but before doing so, she had wanted to gauge the idea's promise with us.

4. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

James P. Malone

James P. Malone

3/14/2008

Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Kathleen C.M. Campbell Art Unit 1614
Serial No. 10/694,436
Filed October 27, 2003
Confirmation No. 8942
For THERAPEUTIC USE OF METHIONINE TO FOR THE TREATMENT OR PREVENTION OF MUCOSITIS
Examiner Shirley V. Gembeh

**DECLARATION UNDER 37 C.F.R. § 1.131**

I, Elizabeth A. Peralta declare as follows:

1. I am an assistant professor in the Division of General Surgery, Department of Surgery at the Southern Illinois University School of Medicine. I received my medical degree from the University of California in Irvine. I completed my general surgery residency at Virginia Mason Medical Center in Seattle and then a surgical oncology fellowship at the City of Hope National Medical Center in California. While in California, I served as Education Committee Chair for the Susan G. Komen Breast Cancer Foundation Los Angeles Affiliate. I am board certified in general surgery. My surgical interests include breast cancer, gastrointestinal tumors and melanoma.

2. On October 17, 2002, I met with Dr. Campbell, but Dr. Malone did not attend. Therefore, Dr. Campbell and I discussed her idea of using methionine as a protectant agent for mucositis arising from radiation therapy. Because I do not treat head and neck cancer patients, we primarily discussed Dr. Campbell's D-methionine protection (particularly otoprotection, neuroprotection and nephroprotection) from the side effects of cisplatin chemotherapy in women with ovarian cancer. I asked Dr. Campbell whether it was possible to use methionine as a protectant for breast cancer patients, but since platinum chemotherapeutic compounds are rarely used to treat breast cancer, Dr. Campbell told me that she didn't think that would be a likely target population. We then agreed to schedule a meeting for Dr. Malone, Dr. Campbell and myself in order to

include Dr. Malone's input regarding head and neck oncology to advance Dr. Campbell's research idea.

3. On November 12, 2002, Dr. Malone, Dr. Campbell, and I focused on how we might test methionine to prevent and/or treat radiation-induced oral mucositis and the accompanying dry mouth. Dr. Campbell discussed the putative mechanisms of methionine protection of normal cells. Dr. Malone talked about animal models and particularly the hamster cheek pouch model. Drs. Campbell and Malone asked for my input regarding therapeutic radiation facilities for animal research. Dr. Campbell discussed her difficulty in obtaining access to therapeutic radiation facilities for her previous research in radiation-induced hearing loss and stated that she was uncertain that she could conduct the animal experiments at SIUSOM because she believed there were no therapeutic research facilities for animals. I stated that although I did animal oncology research, I had not been working with radiation and didn't know whether it was possible to conduct such experiments at SIUSOM. We also discussed possible tumor models to test if methionine's protectant efficacy was selective for healthy tissue or if it also protected tumor cells. I stated that I had never worked with head and neck cancer cell lines or tumor models. Dr. Malone stated that he would be willing to help set up those models, but he did not have much time available. Dr. Malone and I encouraged Dr. Campbell to test methionine as a protectant against radiation-induced oral mucositis. Dr. Campbell told us that she would discuss the idea with scientists from Molecular Therapeutics when she met with them later that week, but before doing so, she had wanted to gauge the idea's promise with us.

4. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Elizabeth A. Peralta — 3/15/08

Elizabeth A. Peralta — Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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|---|---|
| In re application of: | Confirmation No.: 8942 |
| Kathleen C.M. CAMPBELL | Art Unit: 1614 |
| Appl. No.: 10/694,436 | Examiner: Gembeh, Shirley V. |
| Filed: October 27, 2003 | |
| For: **Therapeutic Use of Methionine for the Treatment or Prevention of Mucositis** | |

## Declaration Under 37 C.F.R. § 1.131 Of Alnawaz Rehemtulla, Ph.D.

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

I, Alnawaz Rehemtulla, declare and state as follows:

2. I am a Professor of Radiation Oncology and Radiology at the University of Michigan. I am a Co-Director of the Center for Molecular Imaging at the University of Michigan.

3. I am also a paid consultant for Molecular Therapeutics, Inc. (MTI), which is the licensee of the above-captioned patent application.

4. I received a Bsc. in Molecular Biology at the University of Calgary in 1982, an Msc. in Bacterial Genetics from the University of Calgary in 1984, and a Ph.D. in Immunology from the University of Calgary in 1987. From November, 1987 to August, 1990, I was a Postdoctoral Fellow at the Scripps Clinic and Research Foundation in La Jolla, California. A copy of my *curriculum vitae* is attached.

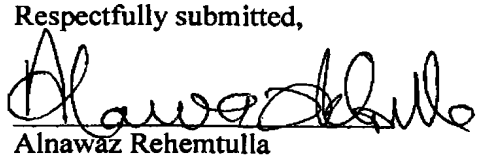
5. On about November 14, 2002, I was present at a meeting between Prasad Sunkara, then CEO of MTI, and Kathleen C.M. Campbell, the inventor of the above-captioned application. The meeting was held at the offices of MTI. At that meeting, Dr. Campbell asked whether experiments could be carried our at MTI to test Dr. Campbell's hypothesis that methionine could protect against radiation-induced oral mucositis.

6. Thereafter, experiments were carried out my me to test Dr. Campbell's hypothesis. To assay the sensitivity of human salivary gland cells to radiation, cultured human salivary gland cells were exposed to ionizing radiation and were simultaneously treated with various concentrations of D-methionine, as shown in the first panel of the attached Exhibit. The data in the first panel of the attached Exhibit reflect the growth rate of the cells over a period of 8 days. It can be seen that each concentration of D-methionine provided a protective effect on the cells. This experiment took nine days to complete, and there was continuous activity over that period. The experiment began prior to March 13, 2003, and was completed by March 19, 2003. The attached Exhibit was created on March 19, 2003.

7. The protective effect of D-methionine observed in this *in vitro* model is reasonably predictive of the effect of D-methionine in humans, *i.e.*, that D-methionine would provide a protective effect against oral mucositis in a human exposed to radiation.

8. I further declare that the above statements made of my own knowledge are true and the above statements based on information and belief from the document discussed are believed to be true. Additionally, I declare that these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under Title 18 United States Code 1001, and that willful false statements may jeopardize the validity of this application or any patent issuing therefrom.

Respectfully submitted,



Alnawaz Rehemtulla

13 MARCH 2008

Date

777729

M+R

| | Day1 | Day2 | Day3 | Day4 | Day5 | Day6 | Day7 | Day8 | Day9 |
|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 3.03 | 4.66 | 9.6 | 12.2 | 26.92 | 42.07 | 58.07 | 60.02 | 55 |
| D-METH | 2.97 | 3.97 | 8.43 | 11.01 | 23.12 | 38.06 | 50.01 | 53.02 | 46.02 |
| RADIATION | 1.91 | 1.965 | 3.73 | 5.01 | 3.62 | 2.4 | 1.89 | 1.78 | 1.65 |
| M(1mg/ml)+ R | 2.34 | 2.97 | 7.12 | 10.14 | 20.18 | 36.34 | 42.32 | 45.34 | 40.14 |
| M(0.5mg/ml) +R | 2.41 | 2.84 | 7.66 | 10.62 | 20.45 | 31.43 | 41.97 | 47.12 | 42 |
| M(0.2mg/ml) +R | 2.61 | 4.01 | 8.01 | 11.01 | 22.54 | 36.12 | 43.91 | 50.45 | 44.12 |
| M(0.1mg/ml) +R | 3.34 | 4.74 | 8.96 | 11.48 | 21 | 35.24 | 46.32 | 52.41 | 46.31 |

R+M(1h)

| | Day1 | Day2 | Day3 | Day4 | Day5 | Day6 | Day7 | Day8 | Day9 |
|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 3.03 | 4.66 | 9.6 | 12.2 | 26.92 | 42.07 | 58.07 | 60.02 | 55 |
| RADIATION | 1.91 | 1.965 | 3.73 | 5.01 | 3.62 | 2.4 | 1.89 | 1.78 | 1.65 |
| R+M (1mg/ml) | 2.54 | 3 | 7.84 | 9 | 20.45 | 31 | 38 | 50.12 | 40.39 |
| R+M(0.5mg/ ml) | 1.74 | 3.8 | 8.14 | 9.85 | 22 | 28.13 | 40.14 | 52.5 | 42 |
| R+M(0.2mg/ ml) | 2.14 | 3.5 | 8.32 | 11 | 25.2 | 36.86 | 45.12 | 51.15 | 48.13 |
| R+M(0.1mg/ ml) | 2.23 | 3.65 | 8.54 | 10.89 | 24.14 | 38.75 | 49.07 | 52.85 | 46.14 |

R+M(2h)

| | Day1 | Day2 | Day3 | Day4 | Day5 | Day6 | Day7 | Day8 | Day9 |
|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 3.03 | 4.66 | 9.6 | 12.2 | 26.92 | 42.07 | 58.07 | 60.02 | 55 |
| RADIATION | 1.91 | 1.965 | 3.73 | 5.01 | 3.62 | 2.4 | 1.89 | 1.78 | 1.65 |
| R+M (1mg/ml) | 2.84 | 3.2 | 8 | 8.76 | 21.45 | 33 | 37 | 51.34 | 39.12 |
| R+M(0.5mg/ ml) | 1.86 | 3.1 | 7.09 | 9.1 | 21.43 | 27.12 | 38.12 | 51.15 | 41 |
| R+M(0.2mg/ ml) | 2.34 | 3.12 | 8.12 | 10.96 | 24.12 | 35 | 44.13 | 51 | 47.45 |
| R+M(0.1mg/ ml) | 2 | 3.21 | 8.96 | 11.12 | 23.12 | 37.12 | 49.85 | 51.85 | 46 |

R+M (4h)

| Day1 | Day2 | Day3 | Day4 | Day5 | Day6 | Day7 | Day8 | Day9 |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 3.03 | 4.66 | 9.6 | 12.2 | 26.92 | 42.07 | 58.07 | 60.02 | 55 |
| RADIATION | 1.91 | 1.965 | 3.73 | 5.01 | 3.62 | 2.4 | 1.89 | 1.78 | 1.65 |
| R+M (1mg/ml) | 2.96 | 3.1 | 7.64 | 9.1 | 22.32 | 32.8 | 36.45 | 50.12 | 40.12 |
| R+M(0.5mg/ ml) | 1.75 | 2.34 | 7.14 | 8.86 | 22 | 26.34 | 38.96 | 50 | 41.97 |
| R+M(0.2mg/ ml) | 2.12 | 2.58 | 3.32 | 8.96 | 9.23 | 26.12 | 43.01 | 48 | 46.62 |
| R+M(0.1mg/ ml) | 2.96 | 3.1 | 7.64 | 9.1 | 22.32 | 32.8 | 36.45 | 50.12 | 40.12 |

R+M(6h)

| | Day1 | Day2 | Day3 | Day4 | Day5 | Day6 | Day7 | Day8 | Day9 |
|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 3.03 | 4.66 | 9.6 | 12.2 | 26.92 | 42.07 | 58.07 | 60.02 | 55 |
| RADIATION | 1.91 | 1.965 | 3.73 | 5.01 | 3.62 | 2.4 | 1.89 | 1.78 | 1.65 |
| R+M (1mg/ml) | 2.01 | 2.12 | 6.32 | 8.12 | 19.34 | 29.36 | 34.32 | 44.32 | 37.36 |
| R+M(0.5mg/ ml) | 1.6 | 1.97 | 6.23 | 7.14 | 20.03 | 22.12 | 32.14 | 42.3 | 37.12 |
| R+M(0.2mg/ ml) | 1.8 | 2 | 2.34 | 7.32 | 8.14 | 24.3 | 35.2 | 40.3 | 38.31 |
| R+M(0.1mg/ ml) | 1.12 | 2.34 | 8.12 | 9.34 | 19.1 | 30.12 | 38.12 | 46.12 | 32 |

R+M(10min)

| | Day1 | Day2 | Day3 | Day4 | Day5 | Day6 | Day7 | Day8 | Day9 |
|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 3.03 | 4.66 | 9.6 | 12.2 | 26.92 | 42.07 | 58.07 | 60.02 | 55 |
| RADIATION | 1.91 | 1.965 | 3.73 | 5.01 | 3.62 | 2.4 | 1.89 | 1.78 | 1.65 |
| R+M (1mg/ml) | 2.12 | 3.12 | 7.12 | 9.45 | 21.45 | 28.24 | 39 | 51.96 | 38.34 |
| R+M(0.5mg/ ml) | 1.85 | 3.3 | 8.04 | 9.5 | 21 | 33 | 42.32 | 51 | 40 |
| R+M(0.2mg/ ml) | 2 | 3.6 | 8.12 | 10 | 24.2 | 36.02 | 41.97 | 53 | 47 |
| R+M(0.1mg/ ml) | 2.02 | 3.64 | 8.46 | 10.12 | 23.22 | 38.06 | 45.07 | 52.14 | 48.12 |